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Influence of exercise intensity on the on- and off-transient kinetics of pulmonary oxygen uptake in humans

F. Özyener*†, H. B. Rossiter*, S. A. Ward‡ and B. J. Whipp*

**Department of Physiology, St George's Hospital Medical School, Cranmer Terrace, Tooting, London, UK, †Department of Physiology, Uludag University Medical School, Bursa, Turkey and ‡Centre for Exercise Science and Medicine, University of Glasgow, Glasgow, UK*

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1. The maximal oxygen uptake ($\dot{V}_{O_2,peak}$) during dynamic muscular exercise is commonly taken as a crucial determinant of the ability to sustain high-intensity exercise. Considerably less attention, however, has been given to the rate at which $\dot{V}_{O_2}$ increases to attain this maximum (or to its submaximal requirement), and even less to the kinetic features of the response following exercise.

2. Six, healthy, male volunteers (aged 22 to 58 years), each performed 13 exercise tests: initial ramp-incremental cycle ergometry to the limit of tolerance and subsequently, on different days, three bouts of square-wave exercise each at *moderate*, *heavy*, *very heavy* and *severe* intensities. Pulmonary gas exchange variables were determined breath by breath throughout exercise and recovery from the continuous monitoring of respired volumes (turbine) and gas concentrations (mass spectrometer).

3. For *moderate* exercise, the $\dot{V}_{O_2}$ kinetics were well described by a simple mono-exponential function, following a short cardiodynamic phase, with the on- and off-transients having similar time constants (τ_1); i.e. $\tau_{1,on}$ averaged 33 ± 16 s ($\pm$ S.D.) and $\tau_{1,off}$ 29 ± 6 s.

4. The on-transient $\dot{V}_{O_2}$ kinetics were more complex for *heavy* exercise. The inclusion of a second slow and delayed exponential component provided an adequate description of the response; i.e. $\tau_{1,on} = 32 \pm 17$ s and $\tau_{2,on} = 170 \pm 49$ s. The off-transient $\dot{V}_{O_2}$ kinetics, however, remained mono-exponential ($\tau_{1,off} = 42 \pm 11$ s).

5. For *very heavy* exercise, the on-transient $\dot{V}_{O_2}$ kinetics were also well described by a double exponential function ($\tau_{1,on} = 34 \pm 11$ s and $\tau_{2,on} = 163 \pm 46$ s). However, a double exponential, with no delay, was required to characterise the off-transient kinetics (i.e. $\tau_{1,off} = 33 \pm 5$ s and $\tau_{2,off} = 460 \pm 123$ s).

6. At the highest intensity (*severe*), the on-transient $\dot{V}_{O_2}$ kinetics reverted to a mono-exponential profile ($\tau_{1,on} = 34 \pm 7$ s), while the off-transient kinetics retained a two-component form ($\tau_{1,off} = 35 \pm 11$ s and $\tau_{2,off} = 539 \pm 379$ s).

7. We therefore conclude that the kinetics of $\dot{V}_{O_2}$ during dynamic muscular exercise are strikingly influenced by the exercise intensity, both with respect to model order and to dynamic asymmetries between the on- and off-transient responses.

The on-transient pulmonary oxygen uptake ($\dot{V}_{O_2}$) response to moderate-intensity square-wave cycle ergometer exercise (i.e. below the lactate threshold, θ_L) has been characterised as mono-exponential (Henry & DeMoor, 1956; Whipp, 1970; Cerretelli & di Prampero, 1987). Above θ_L, the $\dot{V}_{O_2}$ kinetics are more complex (Whipp & Wasserman, 1972; Linnarsson, 1974; Hughson & Morrissey, 1982; Paterson & Whipp, 1991; Barstow & Molé, 1991). Several groups have demonstrated that the 'gain' (i.e. $\Delta\dot{V}_{O_2}/\Delta$WR (work rate)) above θ_L exceeds that for moderate exercise (Whipp & Mahler, 1980; Casaburi *et al.* 1987; Roston *et al.* 1987; Barstow & Molé, 1991; Paterson & Whipp, 1991; Zoladz *et al.* 1995; Tschakovsky & Hughson, 1999), reflecting a greater O_2 'cost' per increment of WR. This supra-θ_L $\dot{V}_{O_2}$ response consists of two components: (a) a 'fundamental' exponential phase and (b) a subsequent phase of delayed onset that yields a slowly developing supplemental rise in $\dot{V}_{O_2}$, resulting in what has been termed 'excess' $\dot{V}_{O_2}$ (Whipp, 1987). However, neither the kinetic features nor the determinants of this additional $\dot{V}_{O_2}$ component have been

Table 1. Subject characteristics

Subject	Age (years)	Height (cm)	Weight (kg)	$\dot{V}_{O_2,peak}$ (l min^{-1})	$\dot{V}_{O_2,peak}$ (ml kg^{-1} min^{-1})	θ_L (ml kg^{-1} min^{-1})
1	58	183	86	2.90	33.7	20.9
2	23	175	70	3.60	51.4	25.7
3	22	185	86	3.85	44.1	26.7
4	22	170	78	3.80	49.3	30.1
5	23	172	58	2.65	45.6	31.0
6	36	178	76	3.61	47.5	25.0
Mean	30.7	177.2	75.7	3.40	45.3	26.5
± S.D.	14.5	5.9	10.6	0.5	6.2	3.7

justifiably established with respect to specific exercise intensity domains.

The $\dot{V}_{O_2}$ off-transient response for moderate exercise has also been characterised by a first-order model similar to that of the on-transient, incorporating a single time constant (τ), delay (δ) and amplitude (A) (Linnarsson, 1974; Paterson & Whipp, 1991). However, the supra-θ_L off-transient kinetics have been reported to be faster than those of the on-transient (Cerretelli *et al.* 1977; Paterson & Whipp, 1991; Gerbino *et al.* 1996; MacDonald *et al.* 1997; Langsetmo & Poole, 1999). Interestingly, this off-transient response was found to be well described by either a mono-exponential function or a double exponential incorporating a slow component that was appreciably smaller in amplitude than for the on-transient. That is, the off-transient $\dot{V}_{O_2}$ kinetics may retain first-order characteristics, despite the work rate exceeding θ_L (Linnarsson, 1974; Paterson & Whipp, 1991; Gerbino *et al.* 1996; Bohnert *et al.* 1998; Langsetmo & Poole, 1999). Since symmetry is an essential feature of linear control system dynamics (e.g. Milsum, 1966), we were interested in examining the degree to which the 'on–off' symmetry of the $\dot{V}_{O_2}$ kinetics was preserved (or not) for a range of physiologically defined exercise intensities. The assignment of exercise intensities, *a priori*, was: (a) moderate (sub-$\hat{\theta}_L$); (b) heavy, for which steady-states in both the increased arterial blood lactate ([L$^-$]) and $\dot{V}_{O_2}$ responses is expected; (c) very heavy, for which continuous increases in both the [L$^-$] and $\dot{V}_{O_2}$ responses is expected, and (d) severe, reflecting work rates requiring steady-state $\dot{V}_{O_2}$s in excess of the $\dot{V}_{O_2,peak}$.

METHODS

Subjects and procedures

Six healthy subjects (Table 1), recruited from the Medical School community, volunteered to take part in the study, after providing signed informed consent approved by the Local Research Ethics Committee (St George's Hospital) and in accordance with the Declaration of Helsinki. Subjects each performed 13 exercise tests on an electro-magnetically braked cycle ergometer (Excalibur Sport, Lode, Groningen, The Netherlands), each on different days. An incremental ramp test (15 W min^{-1}) to the limit of the tolerance was first completed. This allowed the peak $\dot{V}_{O_2}$ ($\dot{V}_{O_2,peak}$) to be established and the lactate threshold to be estimated ($\hat{\theta}_L$) using standard, non-invasive, gas exchange criteria (Beaver *et al.* 1981; Whipp *et al.* 1986). Subjects subsequently exercised three times at four different work rates using a square-wave protocol. The work rates corresponded to: (a) 90 % $\hat{\theta}_L$ (moderate, M); (b) $\hat{\theta}_L$ + 40 % of Δ (heavy, H); (c) $\hat{\theta}_L$ + 80 % of Δ (very heavy, VH); and (d) 110 % of $\dot{V}_{O_2,peak}$ (severe, S) where delta (Δ) is defined as the difference between $\hat{\theta}_L$ and $\dot{V}_{O_2,peak}$. The exercise duration was 10 min for moderate exercise, and 15 min or to the limit of tolerance (whichever was the sooner) at the higher intensities. In all tests, the exercise was preceded by 3–4 min at 20 W, followed by a 20 min recovery also at 20 W (10 min for moderate exercise). We chose light exercise for the control phase of the on- and off-transients as it allowed the actual O_2 cost of the exercise to be related to the actual work rate increment. This obviates the difficulties inherent in estimating the highly variable O_2 cost of the unmeasured work of moving the legs at ~60 r.p.m. Twenty watts was chosen for the WR baseline as the calibrated cycle ergometer work rate was shown to be linear only above this value. All square-wave tests were assigned in a randomised sequence.

Equipment

The subjects breathed through a mouthpiece connected to a low-dead space (90 ml), low resistance (< 1.5 cmH$_2$O at 3 l s^{-1}) turbine volume transducer (Interface Associates, Irvine, CA, USA) for the measurement of inspiratory and expiratory flows and volumes. Respired gas was continuously sampled at 1 ml s^{-1} from the mouthpiece and analysed by mass spectrometry (QP9000, Morgan Medical, Gillingham, UK) for the concentrations of O_2, CO_2 and N_2. Calibration was by two precision-analysed gas mixtures chosen to span the range of inspired and expired gas concentrations. The time delay between the gas concentrations and volume signals was measured by passing a bolus of a known gas mixture through the system using a low dead-space solenoid valve (Beaver *et al.* 1973). The electrical signals were sampled and digitised every 20 ms by computer. Calibrations were also checked immediately after the cessation of each experiment and were indistinguishable from those at the experiment onset.

Modelling

To characterise the kinetics of the $\dot{V}_{O_2}$ response, single and double exponential models (Linnarsson, 1974; Barstow & Molé, 1991) were applied to the data using a non-linear least-squares fitting procedure (Origin, Microcal, USA). The data were then analysed to estimate the system parameters of either single or double exponential models. That is, for the on-transient:

$$\Delta\dot{V}_{O_2(t)} = A_1(1 - e^{-(t-\delta_1)/\tau_1}) \tag{1}$$

or

$$\Delta\dot{V}_{O_2(t)} = A_1(1 - e^{-(t-\delta_1)/\tau_1}) + A_2(1 - e^{-(t-\delta_2)/\tau_2}), \tag{2}$$

where $_1$ and $_2$ denote the 'fundamental' and 'slow' components, respectively, and τ, δ and A the associated time constant, delay and amplitude (i.e. $\Delta\dot{V}_{O_2}$) terms. The amplitude of the slow component for the on-transient (A_2) was characterised to the $\dot{V}_{O_2}$ finally achieved (i.e. the final datum, the last 10 s average of the interpolated responses), and that of the fundamental component (A_1) to its asymptotic value. A_1 and A_2 were also expressed in terms of functional 'gain' ($G = \Delta\dot{V}_{O_2}/\Delta WR$).

For the off-transient:

$$\Delta\dot{V}_{O_2(t)} = A_1\, e^{-(t-\delta_1)/\tau_1} \tag{3}$$

or

$$\Delta\dot{V}_{O_2(t)} = (A_1\, e^{-(t-\delta_1)/\tau_1}) + (A_2\, e^{-(t-\delta_1)/\tau_2}). \tag{4}$$

In the case of eqn (4), the fundamental and slow components were constrained to begin at exercise offset, it being logical to assume that these were both 'in operation' at the start of recovery. Only one δ term (δ_1) was therefore needed.

As the initial, 'cardiodynamic' phase of the $\dot{V}_{O_2}$ response (Phase I; Krogh & Lindhard,1913; Weissman *et al.* 1982) does not directly represent active muscle O_2 utilisation, the first 20 s of the on-transient was omitted from the fitting field. Although the duration of phase I is likely to be less in recovery, as blood flow is higher at the off- than the on-transient, little is known about this duration and therefore omission of the first 20 s of the off-transient was thought to be more than sufficient to obviate any distorting influence on the subsequent kinetics.

Editing of data was only performed to exclude occasional errant breaths caused by swallowing, coughing, sighing, etc., which were considered not to be reflective of the underlying kinetics; i.e. only values greater than 4 standard deviations from the local mean were omitted (Lamarra *et al.* 1987; Rossiter *et al.* 2000). The individual breath-by-breath $\dot{V}_{O_2}$ responses for the three repetitions were then interpolated on a second-by-second basis, ensemble-averaged and time-averaged to produce a standard weighted response at 10 s intervals, thereby reducing the 'noise' and increasing the confidence of the parameter estimation.

The variation of a single bout to the averaged response was analysed both in absolute 'error' and percentage 'error' terms. Any differences across intensity, phase or on- and off-transients were established using ANOVA and the differences of the like responses were grouped. The normalcy of these distributions were determined by probability density, allowing their standard deviations to be established.

Statistics

Comparison between models was based on mean square residual tests for both on- and off-transients. ANOVA and *post hoc* Neuman-Keuls tests were used to discern any differences in the kinetic parameters among the four intensity domains. These were considered significant if $P < 0.05$. The dispersion about the mean is expressed as $\pm$ standard deviation (S.D.), unless otherwise specified.

RESULTS

Steady states of $\dot{V}_{O_2}$ were attained at both moderate (M) and heavy (H) intensities. However, a steady state was not apparent until approximately 10 min into the work bout for the heavy exercise, rather than the $\leqslant 3$ min that was typical of the sub-$\hat{\theta}_L$ exercise. In contrast, a steady state was not attained at any time during the very heavy (VH) or severe (S) work rates (Fig. 1). Rather, $\dot{V}_{O_2}$ continued to increase throughout the test until a peak $\dot{V}_{O_2}$ was established, which averaged 3.39 ± 0.50 l min^{-1} (VH) and 3.31 ± 0.43 l min^{-1} (S); these values were not significantly different from those attained during the ramp test (3.40 ± 0.50 l min^{-1}). During the subsequent recovery, $\dot{V}_{O_2}$ returned to pre-exercise values within a few minutes for the moderate intensity, while taking up to ~20 min for the heavy, very heavy and severe intensities (Fig. 1).

Mono-exponential modelling provided an adequate characterisation of the on-transient $\dot{V}_{O_2}$ kinetics for both the moderate and severe exercise intensities. While this characterisation was not improved by using the double-exponential model at these intensities, it did improve the residuals for both the heavy and very heavy intensities. That is, the residuals fluctuated randomly around zero with the double-exponential model (Fig. 2*B*), but presented systematic positive and negative regions when the mono-exponential model was applied (Fig. 2*A*). These results were consistent among the subjects.

On-transient responses

The fundamental time constant for the $\dot{V}_{O_2}$ on-transient ($\tau_{1,on}$) was independent of exercise intensity, averaging

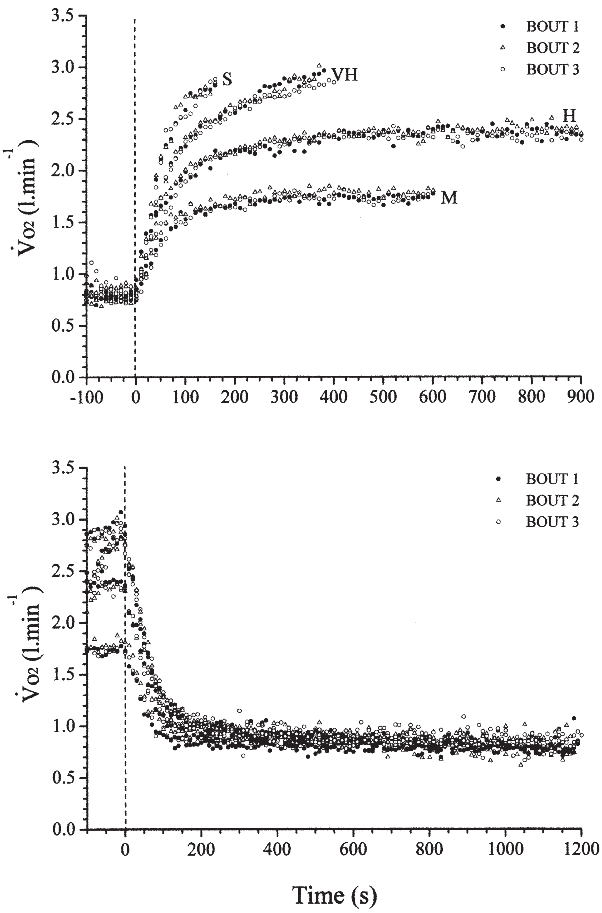

Figure 1

Individual on- and off-transient $\dot{V}_{O_2}$ response profiles (upper and lower panels, respectively) to severe (S), very heavy (VH), heavy (H) and moderate (M) square-wave exercise for a representative subject. The three repetitions at each intensity are displayed.

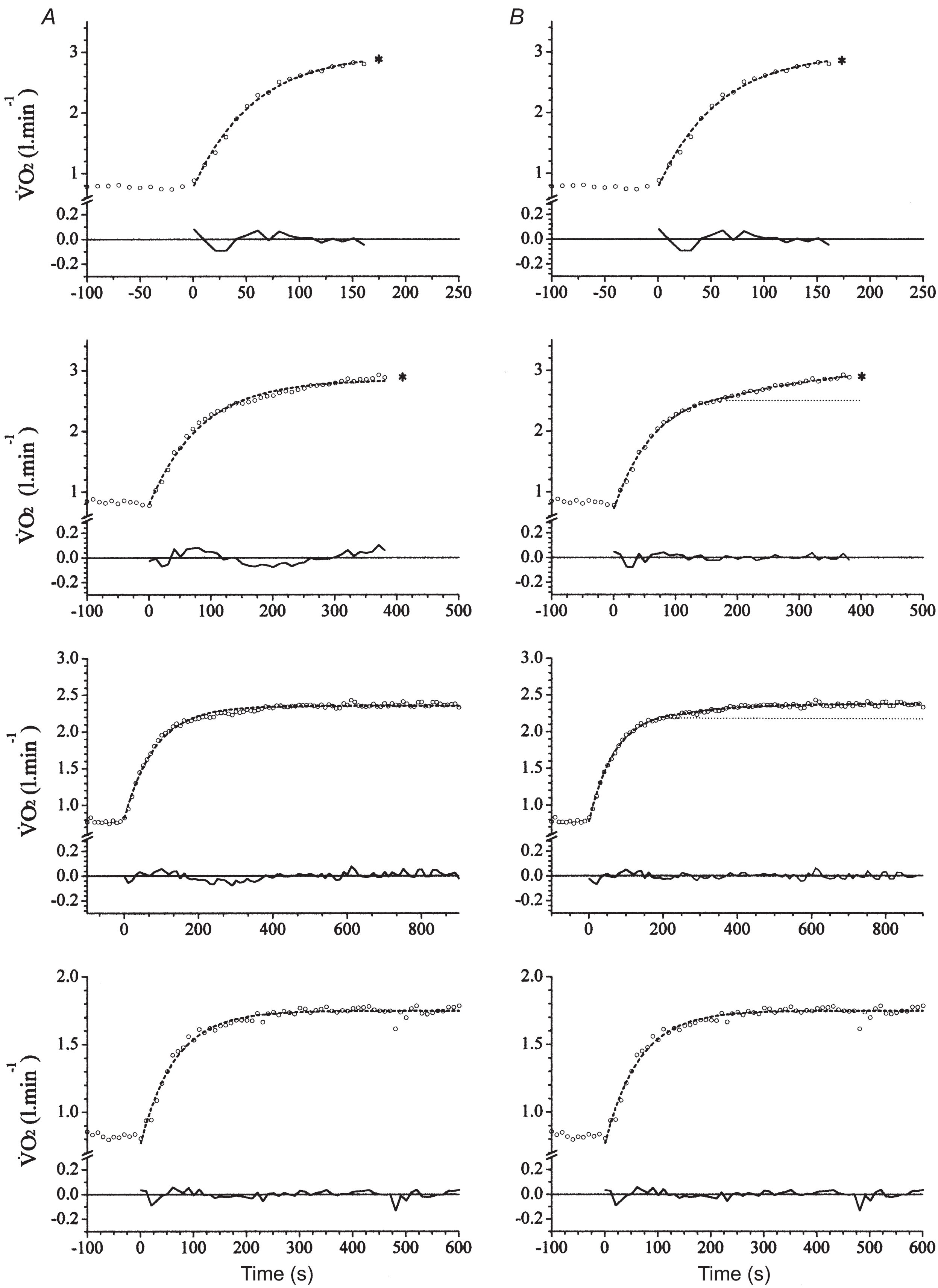

Figure 2. Modelling of the $\dot{V}_{O_2}$ on-transient responses to (from top to bottom) severe, very heavy, heavy and moderate exercise, respectively, for a representative subject, including the corresponding residual plots

A, mono-exponential model. *B*, double-exponential model. * indicates fatigue point for a particular test.

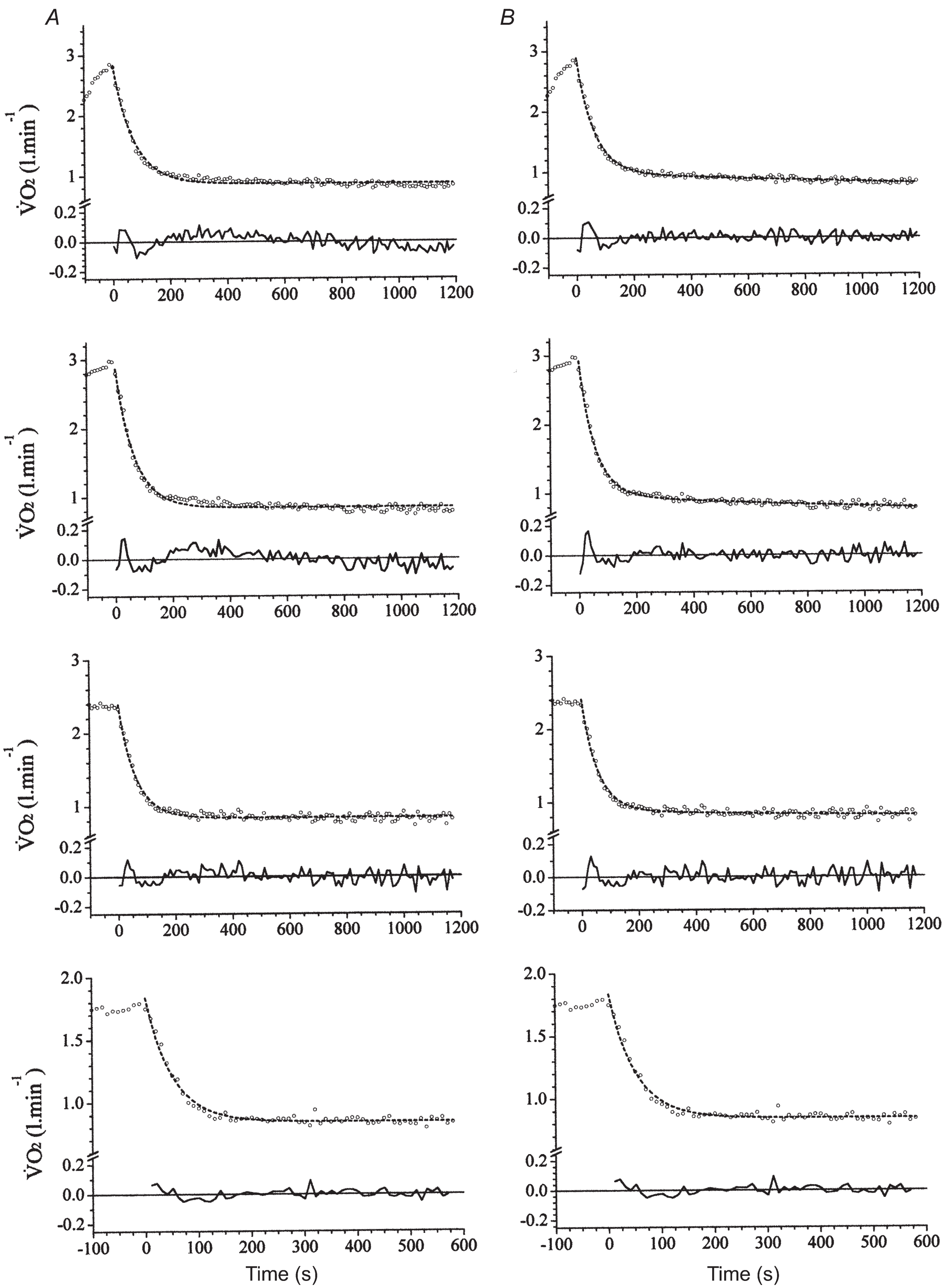

Figure 3. Modelling of the $\dot{V}_{O_2}$ off-transient responses to (from top to bottom) severe, very heavy, heavy and moderate exercise, respectively, for a representative subject

As for Fig. 2.

Table 2. Effect of exercise intensity on the gain of the fundamental (G_1) and total (G_{TOT}) $\dot{V}_{O_2}$ responses for on- and off-transients

	$G_{1,on}$				$G_{1,off}$				$G_{TOT,on}$		$G_{TOT,off}$	
	M	H	VH	S*	M	H	VH	S*	H†	VH†	VH‡	S*
1	11.54	11.87	11.22	10.20	11.32	12.18	11.24	8.71	12.82	13.64	13.07	9.72
2	11.45	10.85	10.77	10.35	11.36	12.30	12.44	7.36	12.02	14.53	14.60	9.83
3	11.47	11.04	10.74	9.81	11.60	12.73	10.66	7.92	13.10	12.17	12.53	9.48
4	11.36	11.67	11.01	10.20	11.15	11.80	11.06	7.82	12.59	12.94	12.50	8.62
5	12.93	9.70	10.30	10.49	11.62	12.87	11.97	8.83	13.22	12.12	13.99	10.00
6	10.34	10.98	10.26	8.91	10.68	11.77	10.75	6.44	11.66	12.57	12.54	8.60
Mean	11.52	11.02	10.72	9.99	11.29	12.28	11.35	7.85	12.57	13.33	13.21	9.30
± S.D.	0.83	0.72	0.38	0.49	0.35	0.35	0.71	0.89	0.62	0.92	0.89	0.56

All values are given in ml min^{-1} W^{-1}. M, moderate; H, heavy; VH, very heavy; S, severe exercise intensities. * $P < 0.05$, smaller than other exercise intensities within group. † $P < 0.05$, greater than $G_{1,on}$ at all intensities. ‡ $P < 0.05$, greater than $G_{1,off}$ M and H intensities.

Table 3. Effect of exercise intensity on the time constant of the fundamental (τ_1) and slow component (τ_2) of the $\dot{V}_{O_2}$ responses for on- and off-transients

	$\tau_{1,on}$				$\tau_{1,off}$				$\tau_{2,on}$		$\tau_{2,off}$	
	M	H	VH	S	M	H	VH	S	H†	VH†	VH‡	S‡
1	58	64	52	44	40	57	43	53	151	200	524	1000
2	32	21	27	32	28	43	31	22	138	152	604	185
3	27	35	43	35	28	52	30	36	178	135	417	439
4	17	21	25	34	21	31	28	41	142	89	245	460
5	48	19	31	38	32	39	32	33	145	203	510	1000
6	18	29	25	23	30	32	31	25	266	199	462	150
Mean	33	32	34	34	29	42	33	35	170	163	460	539
± S.D.	16	17	11	7	6	11	5	11	49	46	123	379

All values are given in seconds. M, moderate; H, heavy; VH, very heavy; S, severe exercise intensities. † $P < 0.05$, greater than $\tau_{1,on}$ at all intensities. ‡ $P < 0.05$, greater than $\tau_{1,off}$ at all intensities.

33 ± 16, 32 ± 17, 34 ± 11 and 34 ± 7 s for the M, H, VH and S intensities, respectively. The functional 'gain' of the fundamental phase ($G_{1,on}$, i.e. $A_{1,on}/\Delta WR$) fell within the normal range previously reported for the steady state of moderate cycle ergometer exercise (Wasserman & Whipp, 1975; Hansen *et al.* 1988; Barstow & Molé, 1991). This averaged 11.5 ± 0.8, 11.0 ± 0.7, 10.7 ± 0.4 and 10.0 ± 0.5 ml min^{-1} W^{-1} for the M, H, VH and S intensities, respectively (Tables 2 and 3). There were no significant differences among the M, H and VH intensities. However, the S value was significantly lower than for the other intensities ($P < 0.05$), although still consistent with previously reported values for moderate exercise.

For the work rates at which a $\dot{V}_{O_2}$ slow component was evident in the on-transient, its estimated amplitude ($A_{2,on}$) was considerably greater for the very heavy intensity than for the heavy intensity (413 ± 291 and 224 ± 142 ml min^{-1}, respectively; $P < 0.05$). This 'excess' $\dot{V}_{O_2}$ corresponded to 12% of the fundamental component for the heavy intensity, and 26% for the very heavy intensity. Consequently, the total 'gain' (G_{TOT}) of the on-transient response (i.e. $(A_{1,on} + A_{2,on})/\Delta WR$) increased to 12.6 ± 0.6 ml min^{-1} W^{-1} for heavy exercise, with a further significant increase to 13.3 ± 0.9 ml min^{-1} W^{-1} for the very heavy exercise ($P < 0.05$). In contrast, G_{TOT} for severe exercise was appreciably less than for the heavy and very heavy intensities, as the tolerable duration was too short to allow the onset of a slow component to be discerned.

The time constant for the $\dot{V}_{O_2}$ slow component ($\tau_{2,on}$) was not significantly different at the heavy and very heavy work rates, averaging 170 ± 49 and 163 ± 46 s, respectively (Table 3). However, these values were approximately 5 times greater than those of the corresponding fundamental τ_1 values (see above). It was of interest that there was a trend for the slow component to emerge later (i.e. the delay term, δ_2, being longer) for the heavy exercise (154 ± 55 s), compared with the very heavy exercise (137 ± 28 s); this difference was not statistically significant, however. Furthermore, the onset of the slow component did not occur at a constant level of $\dot{V}_{O_2}$, but rather became evident at a significantly higher $\dot{V}_{O_2}$ for the very heavy than for the heavy intensity exercise ($P < 0.05$), i.e. at 2800 ± 400 and 2350 ± 330 ml min^{-1}, respectively.

Off-transient responses

The characteristics of the off-transient $\dot{V}_{O_2}$ kinetics for the four exercise intensities differed from those of the on-transient. That is, the mono-exponential model was adequate to characterise the off-transient responses for the moderate and heavy exercise intensities (Fig. 3*A*), whereas a double-exponential was required for the very heavy and severe intensities (Fig. 3*B*). Therefore, it was only for the very heavy intensity that the double-exponential model provided a better description of both the on- and off-transients. However, the off-transient time constant of the fundamental $\dot{V}_{O_2}$ component ($\tau_{1,\mathrm{off}}$) did not vary significantly among the four work intensities, averaging 29 ± 6, 42 ± 11, 33 ± 5 and 35 ± 11 s for the M, H, VH and S intensity domains, respectively (Table 3).

The group-mean off-transient 'gain' ($G_{1,\mathrm{off}}$) was 11.3 ± 0.4, 12.3 ± 0.4, 11.4 ± 0.7 and 7.9 ± 0.9 ml min^{-1} W^{-1} for M, H, VH and S exercise, respectively (Table 2). These values did not differ significantly from those estimated during the on-transient for the M, H and VH intensities (Table 2). It should be noted, however, that the low 'gain' found during the severe exercise was an artefact of the on-transient response. That is, as the $\dot{V}_{O_2}$ on-transient attained $\dot{V}_{O_2,\mathrm{peak}}$ prior to expression of the fundamental asymptote, the off-transient amplitude would necessarily be lower than predicted; i.e. the off-transient $\dot{V}_{O_2}$ response projected to the recovery control level from a value that was necessarily less than the actual $A_{1,\mathrm{on}}$ value.

For the $\dot{V}_{O_2}$ slow component in the off-transient, which was evident only at the very heavy and severe intensities, the time constant ($\tau_{2,\mathrm{off}}$) was longer for the severe (539 ± 379 s) than for the very heavy intensity (460 ± 123 s); this difference was not statistically significant, however (Table 3). These off-transient τ_2 values were several minutes longer (i.e. slower) than those of the corresponding fundamental time constant ($\tau_{1,\mathrm{off}}$) (see above).

Reproducibility

Our results also allowed us to assess the reproducibility of the three repetitions at each of the four exercise

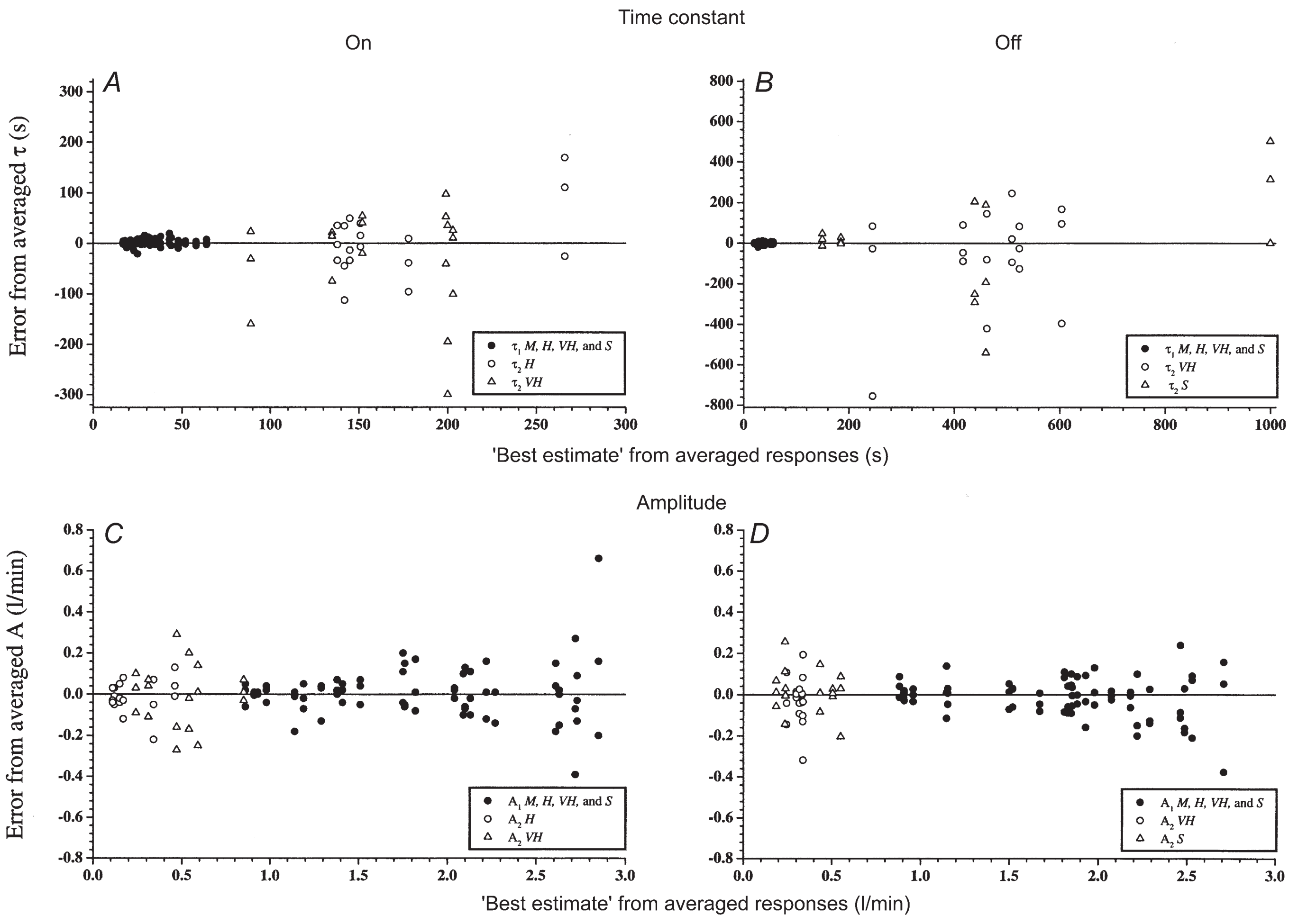

Figure 4. Reproducibility of the $\dot{V}_{O_2}$ time constants (τ_1 and τ_2) and amplitudes (A_1 and A_2) during the on- and off-transients at all intensities

The results are shown as the absolute error of a single bout from the parameters estimated from the averaged $\dot{V}_{O_2}$ response. *A* and *B* give the on- and off-responses of τ and *C* and *D* the on- and off-responses of amplitude.

intensities for both the on- and off-transients. An example of the temporal profile of the $\dot{V}_{O_2}$ responses for a typical subject is presented in Fig. 1. While the general features of the responses were similar between each of the three repetitions at a given exercise intensity, the kinetic parameters estimated from the model fits showed considerable variation. This was most apparent at those exercise intensities that manifested a slow phase of $\dot{V}_{O_2}$. The variations observed in the estimations of the τ and A values between the 'best estimate' of the averaged response profile and the values determined from an individual bout were found to be well characterised by a normal distribution. No significant difference could be established between the variations of τ_1 at the different intensities and the A_1 and A_2 values at all intensities; therefore the τ_1 values were grouped and treated as one population ($n = 72$), τ_2 values were treated as a second population ($n = 36$) and all A values (A_1 and A_2) were consequently treated as one population ($n = 108$). The on- and off-transients were analysed separately. The amplitudes of the three repetitions were found to express a constant variation across all intensities and phases (e.g. Fig. 4), i.e. both the fundamental component (A_1) and the slow component (A_2) expressed similar absolute variation. The standard deviation averaged ~90 ml min^{-1} during the on- and ~60 ml min^{-1} during the off-transient. However, as the magnitude of the mean of the A_2 values were typically one quarter of those of the fundamental (A_1) this variation led to an average 4.2 and 3.8 % 'error' of $A_{1,on}$ and $A_{1,off}$, respectively, and 27.3 and 22.6 % for $A_{2,on}$ and $A_{2,off}$, respectively (Fig. 4*C* and *D*). In contrast, the differences in the estimation of the time constant from the averaged responses were independent of intensity but dependent on phase (i.e. τ_1 was highly reproducible but τ_2 values were not). The resulting standard deviation of τ_1 was 6.2 and 4.0 s for the on- and off-transient fundamental components. The slow component, however, was expressed with a standard deviation of 34.6 and 121.7 s for τ_2 of the on- and off-transients, respectively (Fig. 4*A* and *B*). It should be noted that the on-transient S.D. for this parameter is based on values established from heavy and very heavy exercise whereas the off-transient is established from values of the very heavy and severe domains, i.e. the intensities at which they were expressed. Thus, the off-transient time constant of the slow component ($\tau_{2,off}$) was so highly variable that values of close to 15 min were estimated in some individual bouts (similar to those demonstrated by Linnarsson, 1974, at equivalent intensities), whereas the averaged values were often less than half of this.

DISCUSSION

We have, in this study, determined the characteristic $\dot{V}_{O_2}$ response dynamics to square-wave exercise and recovery as a function of exercise intensity, chosen *a priori*. A single exponential provided appropriate characterisation of both on- and off-transient responses for moderate exercise, with no difference in the response time constant, whereas a double-exponential was required at both the on- and off-transient only for very heavy exercise. For heavy exercise, two such components were evident at the on-transient, but only one at the off-transient. For severe exercise, only a single component was discernible at the on-transient but two were clearly apparent at the off-transient.

During the on-transient of heavy intensity exercise, the fundamental and slow components were both well described by exponential functions, separated in time by a delay of approximately 154 s. The influence of the slow component was not discernible during the off-transient, however. This asymmetry of the $\dot{V}_{O_2}$ kinetics has significant implications for the mechanisms of the slow component itself. It suggests that the oxygen costs of the Q_{10} effect and of increased respiratory and/or cardiac work are likely to be of minor, if any, quantitative importance. Each of these factors would be expected to be evident in both the on- and off-transient responses. Similarly, were the slow component to be a manifestation of the recruitment of a metabolic compartment having a single asymptotic gain and time constant (Barstow *et al.* 1996; Bearden & Moffatt, 2000), then we would expect its influence to be evident also at the off-transient of heavy exercise. This was clearly not the case in our study. Rather, the $\dot{V}_{O_2}$ asymmetries of heavy exercise seem more consistent with continued recruitment of additional contractile units throughout the slow phase of the on-transient, as suggested by Shinohara & Moritani (1992) and Poole *et al.* (1994); i.e. the 'gain' factor would operate as a variable rather than as a constant in this region, associated with a time constant having a value which may be closer to that of the fundamental (i.e. $\tau_{1,on}$) than that apparent for the slow component. Were this to be the case, the off-transient time constant might be expected to be close to that of the fundamental and hence not discernibly different from it. One might expect, therefore, that under conditions where the amplitude of the slow component becomes a more appreciable fraction of the overall off-transient response (i.e. during very heavy exercise), this would become discernible as a separate additional component.

A further concern, not previously addressed, relates to the variability of the slow component with respect to its time constant (τ_2) and amplitude (A_2). The absolute variation in the amplitude of response was shown to be independent of intensity and phase, and is thought to be related to the breath-to-breath noise. This has previously been shown to be independent of work intensity and to be of similar magnitude to the variation measured here (Lamarra *et al.* 1987; Rossiter *et al.* 2000). This time constant, however, proved to be highly variable among and within subjects both at the heavy and the very heavy exercise intensities (Fig. 4*A* and *B*). Consequently, there is a relatively low likelihood of the τ_2 value established on a single transition being sufficiently representative of the 'true' underlying response kinetics of the $\dot{V}_{O_2}$ slow component. Judgements about the appropriateness of this simple first-order structure for the slow component are predicted on the assumption that the input is work rate, or a close proxy of it. Whether this is actually the case cannot be resolved unequivocally at present, given the debate that surrounds the identity of putative mediators. These include: blood lactate concentration (Poole *et al.* 1994); the influence of the metabolic acidosis on the oxyhaemoglobin dissociation curve via the Bohr shift (Wasserman *et al.* 1991); progressive recruitment of fast-twitch muscle fibres (Coyle *et al.* 1992; Shinohara & Moritani, 1992); and increased respiratory and cardiac muscle work (Aaron *et al.* 1992; Stringer *et al.* 1997; Harms *et al.* 1998). Less likely to be significantly involved are increased levels of circulating catecholamines, and increased muscle temperature; neither lead to a discernible increase in the $\dot{V}_{O_2}$ slow component (Gaesser *et al.* 1994; Koga *et al.* 1997). Interestingly, however, Zoladz *et al.* (1998) have reported that the prior induction of a metabolic acidosis by ammonium chloride ingestion increased the magnitude of the slow component, although metabolic alkalosis resulting from sodium bicarbonate ingestion was without effect (Zoladz *et al.* 1997). Consequently while the mechanism(s) of the slow-component are at present poorly understood, it is difficult to postulate why it may differ so markedly with ostensibly the same work rate stimulus.

The fitting strategy employed for characterisation of the $\dot{V}_{O_2}$ slow component has important implications for interpreting the system operation in the supra-θ_L domain, particularly with reference to the computation of the O_2 deficit. We, as others, have characterised the on-transient slow component arbitrarily in terms of single time constant and amplitude values which provides us with what may be termed parameters of 'convenience' (i.e. τ_2 and A_2). As discussed above, however, we do not believe that the A_2 value in this equation need be constant nor that the τ_2 value need be that of the additional contractile units recruited; i.e. the equation for the slow phase (eqn (2)) should not be interpreted in the same manner as for the fundamental component (i.e. eqn (1)).

Interestingly, however, the magnitude of the slow component of the $\dot{V}_{O_2}$ kinetics during recovery seems not to be determined by either the size of the on-transient slow component nor by the absolute metabolic demands of the exercise itself. Cunningham *et al.* (2000), for example, studied the off-transient $\dot{V}_{O_2}$ kinetics when a particular high-intensity end-exercise $\dot{V}_{O_2}$ had been achieved with a range of work rates over which the magnitude of the slow component contributing to that on-transient $\dot{V}_{O_2}$ response was highly variable. The off-transient $\dot{V}_{O_2}$ kinetics were shown to be independent of the on-transient slow-component contribution. In our study, similarly, there was no significant difference in $\tau_{2,\text{off}}$ for the very heavy and the severe intensities, supporting the hypothesis of Cunningham *et al.* (2000) that the absolute $\dot{V}_{O_2}$ achieved (or mechanisms proportionally coupled to it) seems to be the dominant influence on the order of the off-transient kinetics.

In the very heavy exercise domain, a steady state in $\dot{V}_{O_2}$was not achieved. This is consistent with the findings of Poole *et al.* (1990) who demonstrated that the critical power value (Monod & Scherrer, 1965; Hill, 1993) was associated with the maximum sustainable $\dot{V}_{O_2}$. This occurred at some 50–60 % of Δ (i.e. $\dot{V}_{O_2,\text{peak}} - \hat{\theta}_L$), very heavy exercise in our study being chosen to be 80 % Δ. As previously discussed (Whipp, 1987; Poole *et al.* 1988; Whipp & Özyener, 1998), therefore, it was not possible in this domain for a subject to perform a constant work rate that provided a sustained $\dot{V}_{O_2}$ equivalent to a particular percentage of $\dot{V}_{O_2,\text{peak}}$. The time constant of the off-transient slow component ($\tau_{2,\text{off}}$) for very heavy exercise was systematically longer than that for the on-transient. In addition, the off-transient slow component was manifest with no delay. Other investigators have also demonstrated a significant slow phase in the off-transient $\dot{V}_{O_2}$ kinetics for prolonged high-intensity exercise, which becomes more prominent the higher the work rate (e.g. Margaria *et al.* 1933; Knuttgen, 1962; Davies *et al.* 1972; Linnarsson, 1974; di Prampero *et al.* 1989). However, the intensities to which the imposed work rates corresponded in these studies are uncertain. In contrast, the present analysis demonstrates that the $\dot{V}_{O_2}$ slow component becomes demonstrable in recovery at higher absolute supra-$\hat{\theta}_L$ work rates than for the on-transient.

With respect to severe exercise, we could not distinguish between whether the lack of a $\dot{V}_{O_2}$ slow component during the on-transient reflected the short tolerable duration of exercise (i.e. shorter than that required to induce the slow-component), or whether the slow component is difficult to discriminate in a region that is proportionally dominated by the fundamental component. It should be noted that, in our study, the slow component was not evident until 154 s after exercise onset for the heavy intensity and 137 s for the very heavy exercise, whereas the total duration of the severe exercise test was only of the order of 150 s. However, in light of the fact that the on-transient delay term for the $\dot{V}_{O_2}$ slow component (δ_2) tended to be reduced as exercise intensity increased, coupled with a large and clearly distinguishable slow component in the subsequent recovery, we favour the latter suggestion. However, further work is warranted on this issue.

A further possible explanation for the on–off asymmetry in the $\dot{V}_{O_2}$ kinetics could be that routes of lactate metabolism, for example, may differ according to the exercise intensity. The sustained increase in lactate concentration during supra-θ_L exercise (and the transient, or 'early', lactate increase during moderate exercise; Cerretelli *et al.* 1979; Cerretelli & di Prampero, 1987) may require different mechanisms for its subsequent metabolism (Bertram *et al.* 1967; Krisanda *et al.* 1988; Gladden, 1996) that are themselves intensity dependent. Any lactate cleared oxidatively during recovery may not be seen as an additional kinetic component in $\dot{V}_{O_2}$ if the lactate metabolism follows the same mitochondrial pathways utilised during moderate exercise. In contrast, any lactate that serves as a source for glyconeogenesis (in liver and, it appears, skeletal muscle) has an obligatory additional oxygen cost as expressed in the Meyerhof quotient (Meyerhof, 1920; Krebs & Kornberg, 1957). Similarly, any lactate-derived reducing equivalents that are transported into the mitochondrion as an aerobic source that utilises the α-glycerophosphate shuttle rather than the malate–aspartate shuttle (Schantz & Henriksson, 1987) would also incur an additional O_2 demand during recovery (Whipp, 1987). This component is more likely to contribute at high lactate concentrations. Consistent with this view is the observation of Roth *et al.* (1988) in humans that when blood [lactate] was increased to 4–5 mM by occluding limb blood flow, there was no discernible additional recovery O_2 cost. Similarly, Whipp (1987) demonstrated that the magnitude of the $\dot{V}_{O_2}$ slow phase became appreciably greater above these blood lactate levels. We are not aware, however, of the energetic consequences related to the transport of lactate itself into the mitochondrion (Brooks *et al.* 1999).

Interestingly, we could not find a significant influence of work intensity on τ_1 for $\dot{V}_{O_2}$ at the on-transient among moderate, heavy and very heavy intensities. This is consistent with the previous findings of Barstow & Molé (1991). In contrast, Paterson & Whipp (1991) and, more recently, Koga *et al.* (1999) have reported τ_1 to be longer for heavy than for moderate exercise. The differences in these findings could represent different metabolic characteristics of different individuals in the sample group. For example, some of the subjects from the Barstow & Molé study (1991) did show an intensity-dependent difference in τ_1, and some subjects from the Paterson & Whipp study (1991) did not. It is not clear whether this was also the case in the more recent study of Koga *et al.* (1999) – although the S.D. of the mean response was sufficiently large at both moderate and heavy intensities to suggest that this might also be the case. The results of the present study are consistent with this supposition.

A degree of uncertainty surrounds the reproducibility of the $\dot{V}_{O_2}$ kinetics for the fundamental component in the exercise on-transient. While the individual τ_1 values for each of the three different determinations typically varied from the averaged response by up to 10% for the moderate, heavy and very heavy exercise intensities, there was much greater variability among the three individual repetitions for the severe exercise. This presumably reflects the short duration of response available for the fitting procedure at this intensity (Lamarra *et al.* 1987). The influence of the inter-breath 'noise' on the $\dot{V}_{O_2}$ response is reduced by averaging the results of several identical tests in a particular subject (Lamarra *et al.* 1987). It seems likely that 'noise' associated with a single transition could readily account for the 10% variation seen in the individual τ_1 estimates, although the possibility of 'real' variation on different occasions cannot be excluded. In contrast, the corresponding individual A_1 values were essentially identical to their averaged values (in all but the VH and S results of subject 4).

Interestingly, the off-transient $\dot{V}_{O_2}$ kinetics were similarly variable. This suggests that the variability was related to metabolism itself, rather than to factors such as variations in pedalling frequency, additional work performed by upper limb muscles, or other extraneous sources of metabolic demand. That is, these factors might reasonably be more likely to influence the on-transient rather than the off-transient response, during which our subjects cycled comfortably at just 20 W. The variability between repetitions for supra-$\hat{\theta}_L$ exercise for both on- and off-transients may have major implications for inferences that can be drawn from studies which attempt to discriminate between the effect of interventions such as diet (Molé & Hoffman, 1999), training (Hagberg *et al.* 1980), inspired fraction of O_2 (MacDonald *et al.* 1997; Tschakovsky & Hughson, 1999), or even activation of the pyruvate dehydrogenase complex by means of dichloro-acetate (Timmons *et al.* 1998).

In conclusion, the $\dot{V}_{O_2}$ slow components manifest during the on-transient of heavy and very heavy exercise and at the off-transient of very heavy and severe exercise have important implications for assembling control models of human pulmonary gas exchange during square-wave exercise: (a) pulmonary O_2 uptake kinetics are not symmetrical, except for moderate intensity exercise; (b) the total 'gain' term is not constant, i.e. $\Delta\dot{V}_{O_2}$ is not a linear function of work rate; and (c) the assumptions inherent in the conventional means of computing the O_2 deficit during high-intensity exercise need fundamental reappraisal. Adequate control models of the role of exercise intensity on the kinetics of $\dot{V}_{O_2}$ should therefore consider such intensity-dependent features as necessary output responses. Only when this is successfully achieved will it be possible to establish justifiable physiological equivalents of the model parameters.

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Corresponding author

B. J. Whipp: Department of Physiology, St George's Hospital Medical School, Cranmer Terrace, Tooting, London SW17 0RE, UK.

Email: bwhipp@sghms.ac.uk